REMARKS

Claims 1-13 remain pending in this application. Claims 1-11 and 13 are rejected. Claims 8 and 13 and the specification are objected to. Claims 1, 2, 6-11, and 13 have been amended to be in better form. Claims 8 and 9 have been amended to clarify the invention. Claim 4 has been amended to include some of the recitations of claim 5 and such recitations have been removed from claim 5.

The Title has been objected to. The Office Action suggests that the word "novel" be removed from the title. The title is amended herein to remove the word "novel" as suggested by the Examiner.

Claims 8 and 13 have been objected to as having mislabeled steps. Claims 8 and 13 have been amended so that the numbering of the steps is in consecutive order.

Claims 1-11 and 13 have been rejected under 35 U.S.C. § 112, second paragraph, as indefinite.

The Office Action states that in claim 1, the broad recitation of "folding of a biopolymer" and also the narrower recitation of protein folding in the same claim makes the claim indefinite. The language of "folding of a biopolymer" has been changed to "folding of a protein" in claim 1.

The Office Action states that the phrase "such as" in claim 5 renders the claim indefinite. The recitation of "such as" has been removed from claim 5.

The Office Action states that the term "computational manageable number" in claim 8 is a relative term which renders the claim indefinite. The Office Action states that there is no definition in the specification as to what is meant by this term and that one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The language "to a computationally manageable number" has been removed from claim 8.

The Office Action states that the limitation "the optimal β-sheet alignments" in claim 10 does not have proper antecedent basis. The language of "the optimal β-sheet alignments" has been replaced with "optimal β-sheet alignments".

In light of the above amendments, it is Applicants' position that claims 1-11 and 13 are definite and respectfully request that the indefiniteness rejection be withdrawn.

Claims 4-7 have been rejected under 35 U.S.C. § 112, first paragraph, as nonenabled. The Office Action states that there is enablement for topology prediction/estimation but not for functional prediction. The Office Action states that claim 4 is directed to the prediction of loss of function of biological activity based only on predicted protein topology and states that the specification fails to provide the required guidance to support the limitations of claim 4. The Office Action states that the specification also fails to provide examples of

how the loss of biological function is predicted based on the estimated topology. The Office Action states that the current state of the art teaches against the ability to estimate changes in a protein's functionality based on prediction of structure and cites to Tosatto et al., Current Pharmaceutical Design, Vol. 12, 2067-2086, 2006 ("Tosatto et al."). Specifically, the Office Action states that Tosatto et al. teaches that when two proteins share structure, that function cannot be predicted because it may not necessarily be the same and that proteins with different structure may have the same function. The recitation in claim 4 directed to predicting the loss of biological activity of the protein has been removed. Applicants therefore respectfully request that the enablement rejection of claims 4-7 be withdrawn.

Claims 1, 3, 8, and 13 have been rejected under 35 U.S.C. § 102(b) as anticipated by J. theor. Biol, Vol. 213, p. 359-386, 2001 (Dawson et al.).

Claim 1 is directed to a method to predict the topology of the spatial arrangement of an amino acid sequence using an entropy evaluation model that takes into account the global contributions of entropy to the folding of a biopolymer combined with other thermodynamic potentials as a protein-folding model. "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *See Verdegaal Brothers Inc. v. Union Oil Company of California,*

2 USPQ2d 1051, 1053 (Fed. Cir. 1987). The Office Action states, on page 7, that Dawson et al. teach a method to predict the topology of the spatial arrangement of an amino acid sequence and cites to the abstract on page 359 of Dawson et al. Dawson et al., including the abstract, is directed to RNA sequences and, in contrast, claim 1 is directed to amino acid sequences. Accordingly, the Office Action has therefore not demonstrated the anticipation of claim 1.

Furthermore, the purpose of Dawson et al. is to propose a new and more accurate entropy model. Moreover, the present invention utilizes the free energy to predict a structure and there is no disclosure in Dawson et al. for the method of calculating the free energy of an amino acid sequence. Also, there is no disclosure in Dawson et al. on how to build structures, only to analyze given ones. The statement in the abstract of Dawson et al. that the cross linking entropy model can be extended means that the calculation of entropy can be extended. In other words, a method to calculate entropy is what is the focus and there is no teaching of a method to preduct the topology of the spatial arrangement of an amino acid sequence.

Also, secondary structure of RNA includes essential information on the topology of the spatial arrangement of an RNA sequence. Protein secondary structure does not. Protein secondary structure only provides information that a

part of the amino acid sequence is a beta sheet or an alpha helix, but does not provide the information about how it is arranged. The method in Dawson et al. requires the topology of the spacial arrangement of the RNA sequence to make its calculations. Therefore, the method disclosed in Dawson et al. does not address how to find the topology of the spatial arrangement of RNA or proteins. The method disclosed in Dawson et al. only deals with how to calculate the entropy correctly, and this is directed only at RNA and there is no demonstration of its application as applied to proteins. Additionally, Dawson et al. is directed to get rid of faulty entropy calculations and utilize structure and free energy. There is no actual calculation of structure or free energy for proteins. Accordingly, Dawson et al. fails to teach a method to predict the topology of the spatial arrangement of an amino acid sequence.

Claim 3 recites that CLE is used to evaluate the entropy loss of a protein due to folding into a particular topology given a known secondary or estimated secondary structure. The Office Action states that such limitation is disclosed on page 365, col. 2, lines 3-5 of Dawson et al. Page 365, col. 2, lines 3-5 of Dawson et al. does not disclose evaluating the entropy loss of a protein. Dawson et al. is directed to the evaluation of RNA sequences. Accordingly, claim 3 is patentable over the cited art and notice to that effect is respectfully requested.

Claim 8 recites, in step A., inputting an amino acid sequence of a protein. The Office Action states that such limitation is disclosed in Dawson et al. on page 360, column 1, paragraph 3, lines 17-23. Paragraph 3 on page 360 of Dawson et al. does not disclose an amino acid sequence of a protein. As mentioned above, the given RNA secondary structures contain the topology of the spatial arrangements of the RNA. Protein secondary structure does not. The topology of the spatial arrangement of an amino acid sequence is not inputted or given in any way in the method of Dawson et al. In contrast, the present invention finds the topology of an amino acid sequence.

Claim 8 recites, in step E (now step C), applying the CLE method to approximate the global folding kinetics of the amino acid sequence and the Office Action cites to Dawson et al., page 378, column 1, lines 1-3 for this disclosure. Page 378, column 1, lines 1-3 of Dawson et al. fail to disclose applying the CLE method to approximate the global folding kinetics of the amino acid sequence.

Claim 8 includes step G (now step D), which recites applying the CLE method to the amino acid sequence and secondary structure information to reduce the number of combinatorial number of β-strand and α-helix arrangements. The Office Action has not identified how this element of the claim is met in Dawson et al.

Claim 8 includes step H (now step E), which recites applying the CLE method to optimize the free energy to find the most thermodynamically favorable topology for the amino acid sequence. The Office Action has not identified where this step is met by Dawson et al. Furthermore, based on Dawson et al., the RNA structure or protein structure cannot be calculated without being given a structure to calculate and therefore, this element is not met by Dawson et al.

Claim 13 recites, in step A., inputting an amino acid sequence of a protein. The Office Action states that such limitation is disclosed in Dawson et al. on page 360, column 1, paragraph 3, lines 17-23. Paragraph 3 on page 360 of Dawson et al. does not disclose an amino acid sequence of a protein. Claim 3 recites, in step E (now step C), applying the CLE method to approximate the global folding kinetics of the amino acid sequence and the Office Action cites to Dawson et al., page 378, column 1, lines 1-3 for this disclosure. Page 378, column 1, lines 1-3 of Dawson et al. fails to disclose applying the CLE method to approximate the global folding kinetics of the amino acid sequence. Claim 13 includes step I (now step D), which recites using the global folding kinetics to predict the optimal topology of the amino acid sequence. The Office Action has not identified how this element of the claim is met in Dawson et al. Claim 13 includes step F (now step E), which recites storing the information in a data

file or in other form of digital memory. The Office Action cites to Table 2 on page 276 of Dawson et al. for this limitation. Typing information in a table is not the same as storing it in a data file or in other form of digital memory. Furthermore, Table 2 compares two models. It cannot be utilized as an input table or look up table. Moreover, Table 2 reports a comparison of the two methods on a given structure, not one that must be found. Also, the table has nothing to do with "storing information in a data file."

Accordingly, at least for the above-mentioned reasons, it is Applicants' position is that claims 1, 3, 8, and 13 are patentable over Dawson et al. and notice to that effect is respectfully requested.

Claims 2, 4-7, and 9-11 were not rejected under the prior art. Since those claims were not rejected under any prior art, it is Applicants' assumption that the Examiner deems that those claims contain allowable subject matter and notice to that effect is respectfully requested.

Claims 8 and 9 have been amended to clarify the invention. Support can be found, for example, in Step (D) of claim 2 as filed, in claim 11 as filed, in the specification on pages 10-12, on page 17, lines 5-8, on page 23, lines 3-5, on page 32, lines 14-16, and on page 33, lines 2-5.

Applicants respectfully request a two month extension of time for responding to the Office Action. **The fee of $225.00 for the extension is**

provided for in the charge authorization presented in the PTO Form 2038, Credit Card Payment form, provided herewith.

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In light of the foregoing, the application is now believed to be in proper form for allowance of all claims and notice to that effect is earnestly solicited.

Respectfully submitted,

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